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(54) Use of sertraline for the treatment of chemical dependencies.

(57) A method of treating a chemical dependency in a mammal, comprising administering to a mammal in need of such treatment an amount of the compound (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, also known by the generic name sertraline, or a pharmaceutically acceptable salt thereof, effective in reducing or alleviating such dependency.

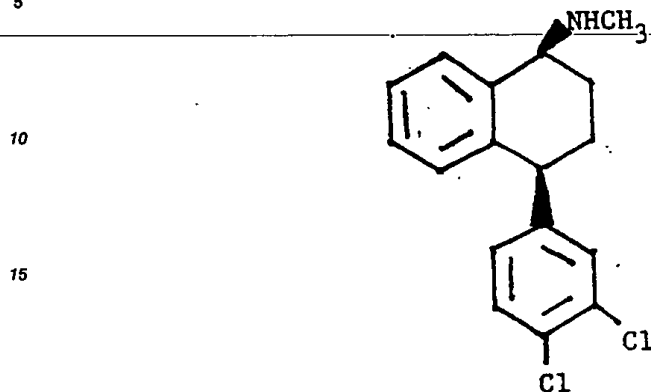
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A METHOD OF TREATING CHEMICAL DEPENDENCIES USING SERTRALINE

This invention relates to a method of treating a chemical dependency in a mammal using the compound (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, hereinafter referred to by its generic name "sertraline", or a pharmaceutically acceptable salt thereof.

Sertraline, which has the empirical formula $C_{12}H_{17}NCl_2$ and the structural formula

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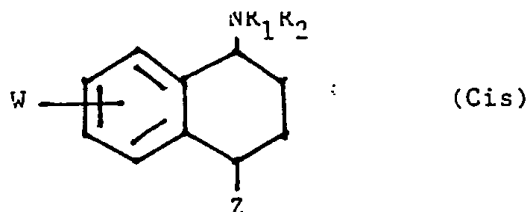
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is a known antidepressant and anorectic agent. United States Patent 4,536,518, assigned in common with the present invention and hereby incorporated herein by reference, discloses sertraline and related compounds of the formula

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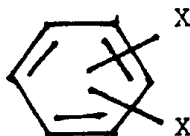
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wherein Z is

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and R_1 , R_2 , W, X and Y are as defined therein, and states that such compounds exhibit antidepressant and anorectic activity in vivo in mammals.

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The present invention relates to a method of treating a chemical dependency in a mammal, comprising administering to a mammal in need of such treatment an amount of sertraline, or a pharmaceutically acceptable salt thereof, effective in reducing or alleviating such dependency. "Chemical dependency," as used herein, means an abnormal craving or desire for, or an addiction to a drug. Such drugs are generally administered to the affected individual by any of a variety of means of administration, including oral, parenteral, nasal or by inhalation. Examples of chemical dependencies treatable by the method of the present invention are dependencies on alcohol, nicotine, cocaine, heroin, phenobarbital, and benzodiazepines (e.g., Valium (trademark)). "Treating a chemical dependency," as used herein, means reducing or alleviating such dependency.

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Examples of pharmaceutically acceptable salts of sertraline that can be used to treat chemical dependencies in accordance with the present invention are the acid addition salts of various mineral and organic acids such as hydrochloric, hydrobromic, hydroiodide, sulfuric, phosphoric, acetic, lactic, maleic, fumaric, citric, tartaric, succinic, and gluconic.

5 Studies performed by the assignee of the present invention indicate that sertraline reduces ethanol intake and ethanol preferences in rats without altering overall fluid intake. Other compounds of the foal may be similarly effective. The usefulness of sertraline and the other compounds of formula I in treating chemical dependencies is neither disclosed in, nor suggested by the prior art.

Sertraline may be prepared as described in United States Patent 4,536,518, and particularly, in
10 Example 2 of that patent.

Sertraline, or a pharmaceutically acceptable salt thereof, when used to treat a chemical dependency, may be administered either orally or parenterally. It is generally administered in dosages ranging from about 50-200 mg per day, although variations will necessarily occur depending upon the condition of the subject being treated and the particular route of administration chosen. It may be administered either alone
15 or in combination with pharmaceutically acceptable carriers by either of the above routes, and such administration can be carried out in both single and multiple dosages. More particularly, sertraline, or a pharmaceutically acceptable salt thereof, may be administered in a wide variety of different dosage forms, i.e., it may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hand candies, powders, sprays, aqueous suspensions, injectable solutions,
20 elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, sertraline, or a pharmaceutically acceptable salt thereof, when used to treat a chemical dependency, is present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of
25 the total composition, i.e. in amounts that are sufficient to provide the desired unit dosage. It may exist in different polymorphic forms, i.e. different crystalline forms.

For purpose of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents
30 such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred fillers would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixers are desired for oral administration, the sertraline, or pharmaceutically
35 acceptable salt thereof, may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions of sertraline, or a pharmaceutically acceptable salt thereof, in sesame or peanut oil or in aqueous propylene glycol or N,N-dimethylformamide may be
40 employed, as well as sterile aqueous solutions of the water-soluble, non-toxic mineral and organic acid addition salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable by standard techniques
45 well-known to those skilled in the art.

A typical dry solid pharmaceutical composition is prepared by blending the following materials together in the proportions by weight specified below:

Cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,
2,3,4-tetrahydro-1-naphthalenamine hydrochloride: 50
50 Sodium citrate: 25
Alginic acid: 10
Polyvinylpyrrolidone: 10
Magnesium stearate: 5

After the dried composition is thoroughly blended, tablets are punched from the resulting mixture, each
55 tablet being of such size that it contains 100 mg of sertraline hydrochloride. Other tablets are also prepared in a similar fashion containing 5, 10, 25, and 50 mg of sertraline hydrochloride respectively, by using the appropriate amount of the naphthalenamine salt in each case.

Another typical dry solid pharmaceutical composition is prepared by combining the following materials

together in the proportions by weight indicated below:

Cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,

2,3,4-tetrahydro-1-naphthalenamine hydrochloride: 50

Calcium carbonate: 20

5 Polyethylene glycol, average molecular weight,

4000: 30

The dried solid mixture so prepared is then thoroughly agitated so as to obtain a powdered product that is completely uniform in every respect. Soft elastic and hard-filled gelatin capsules containing this pharmaceutical composition are then prepared, employing a sufficient quantity of material in each instance so as to

10 provide each capsule with 50 mg of the active ingredient.

Claims

- 15 1. Use of (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine, or a pharmaceutically acceptable salt thereof, for making a medicament for treating a chemical dependency or addiction.
2. Use according to claim 1, wherein the chemical dependency is a dependency on cocaine.
3. Use according to claim 1, wherein the chemical dependency is a dependency on nicotine.
4. Use according to claim 1, wherein the chemical dependency is a dependency on alcohol.
- 20 5. Use according to claim 1, wherein the chemical dependency is a dependency on phenobarbital.
6. Use according to claim 1, wherein the chemical dependency is a dependency on a benzodiazepine.

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

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European Patent
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PARTIAL EUROPEAN SEARCH REPORT

Page 2

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| DOCUMENTS CONSIDERED TO BE RELEVANT | | | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|-------------------------------------|---|-------------------|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | |
| X | CLINICAL NEUROPHARMACOLOGY, vol. 8, no. 4, 1985, pages 299-317, Raven Press, New York, US; L. LEMBERGER et al.: "Use of specific serotonin uptake inhibitors as antidepressants" * Page 302, table 1; pages 311-312 * | 1-6 | |
| P,Y | WO-A-9 004 387 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) * Abstract; page 2; claims 1,3 * | 1-6 | |
| D,A | US-A-4 536 518 (W.M. WELCH et al.) * Abstract; claims 1-3,5,7,15,17,19-22 * | 1-6 | |
| A | PAIN, vol. 21, no. 4, April 1985, pages 329-337, Elsevier Science Publishers B.V.(Biomedical Division), Amsterdam, NL; Y.O. TAIWO et al.: "Potentiation of morphine antinociception by monoamine reuptake inhibitors in the rat spinal cord" * Summary * | 1-6 | TECHNICAL FIELDS SEARCHED (Int. Cl.5) |